

***Remarks***

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-4, 6-8, 41, 72 and 73 are pending in the application, with claims 1 and 73 being the independent claims.

Claims 9-40 and 42-71 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 72 and 73 are sought to be added. Support for the amendments to claim 1 may be found, for example, at page 5, line 22 to page 6, line 18, of the specification. Support for new claim 72 can be found, for example, at page 21, lines 3-4, of the specification. Support for new claim 73 can be found, for example, at page 21, lines 3-13, and from page 22, line 11, to page 25, line 16, of the specification.

These amendments are made to place the claims in better form for allowance or consideration on appeal by materially reducing or simplifying the issues for appeal.

These changes are believed to introduce no new matter, or raise new issues that would require further consideration and/or search. Although the amendments present additional claims, a corresponding number of finally rejected claims have been canceled. Entry of these amendments is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Summary of Final Office Action***

The examiner has noted the need for cancellation of claims withdrawn due to a previously made restriction and election, and has made one rejection under 35 U.S.C. § 112, second paragraph, and three rejections under 35 U.S.C. § 103(a). The Examiner has also made a nonstatutory double patenting rejection.

***Election/Restriction***

The Examiner has indicated that the "application contains claims 9-71 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action . . . ." *See* Office Action, page 2, paragraph 2. Applicants respectfully point out that claims 1-4, 6-8 and 41 were previously elected, consonant with the previously made restriction requirement. *See* Reply to Restriction Requirement, page 1, first paragraph, filed on July 16, 2002; and PTO File Wrapper Paper No. 13, page 2, paragraph 2. This election has also been acknowledged by the Examiner. *See* PTO File Wrapper Paper No. 16, page 2, paragraph 1. Accordingly, Applicants believe that only cancellation of claims 9-40 and 42-71 is necessary to completely reply to the outstanding Office Action. As shown in the ***Amendments to the Claims*** section above, claims 9-40 and 42-71 are cancelled without prejudice to or disclaimer of the subject matter therein.

***Rejections under 35 U.S.C. § 112***

Claims 1-4, 6-8 and 41 are rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention." *See* Office Action, page 2, paragraph 4. In particular, claim 1 is allegedly "vague and indefinite because [the] preamble . . . and final product produced by method steps do not correspond [to] each other." *Id.* at paragraph 5.

Solely to clarify the claims, Applicants have amended the preamble of claim 1 as shown in the ***Amendments to the Claims*** section above. Claim 1 is now directed to a method for hybridizing one or more nucleic acid molecules, the method comprising

i) contacting one or more double-stranded nucleic acid molecules with a denaturant selected from the group consisting of

a) one or more amino acid denaturants,

b) imidazole, and

c) one or more amino acid denaturants plus imidazole,

thereby forming one or more single-stranded nucleic acid molecules; and

ii) combining the one or more single-stranded nucleic acid molecules with one or more nucleic acid molecules wherein the one or more nucleic acid molecules are capable of hybridizing to the single-stranded nucleic acid molecules thereby obtaining one or more of said hybridized nucleic acid molecules.

As the preamble and final product of amended claim 1 correspond to each other,

Applicants respectfully assert that claim 1 and its dependent claims are not indefinite.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-4, 6-8 and 41 under 35 U.S.C. § 112, second paragraph.

***Rejections under 35 U.S.C. § 103***

***Claims 1, 2, 4, 6-8 and 41***

Claims 1, 2, 4, 6-8 and 41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zarling *et al.* (U.S. Pat. No. 5,719,023) in view of Aslanyan *et al.* (*Biophys.*, 29: 615-620 (1984)). See Office Action, page 3, paragraph 7. In particular, the Examiner alleges that

it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Zarling *et al.*, and Aslanyan *et al.*. One having ordinary skill in the art would have been motivated to do so because Aslanyan *et al.*, have successfully used an amino acid denaturant (i.e., glycine) to denature a double stranded nucleic acid probe into a single stranded and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Aslanyan *et al.*,) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

See Office Action, paragraph bridging pages 4-5. Applicants respectfully traverse this rejection.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. In particular, the M.P.E.P. sets forth the criteria necessary to satisfy this burden:

To establish a *prima facie* case of obviousness, three basic criteria *must* be met. First, there *must* be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there *must* be a reasonable expectation of success. Finally, the prior art reference (or references when combined) *must* teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success *must* both

be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

See M.P.E.P., Eighth ed., February revision, § 2142 "Legal Concept of *Prima Facie* Obviousness," (2003, emphasis added). Applicants respectfully assert that the references cited in support of the 35 U.S.C. § 103 rejection do not meet these criteria, and that consequently the Examiner has not established a *prima facie* case of obviousness.

In regard to the first criteria, a *prima facie* case of obviousness has not been made because there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Zarling *et al.* or to combine Zarling *et al.* with Aslanyan *et al.* to arrive at the claimed methodology. The Examiner has acknowledged that Zarling *et al.* fails to disclose denaturing "double stranded nucleic acid molecules using amino acid denaturants as recited in claims 1, 2, 4, 6-8 and 41." See Office Action, page 4, lines 6-7. Moreover, Aslanyan *et al.* makes no reference to denaturing double stranded DNA for the purpose of subsequent hybridization of the strands to different nucleic acid molecules. Absent the teachings in Applicants' specification, the skilled artisan would not regard the denaturation methodology of Aslanyan *et al.* as a substitute or useful in the hybridization methodology discussed by Zarling *et al.* Applicants respectfully assert that the Examiner has improperly relied upon hindsight reasoning.

Relying upon M.P.E.P. §§ 2144.07 and 2144.09, the Examiner alleges that motivation to utilize the denaturation method disclosed by Aslanyan *et al.* in the methodology disclosed by Zarling *et al.* "arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when

combined for their common known purpose." *See* Office Action, p. 5, lines 7-10.

However, as discussed above, Aslanyan *et al.* does not describe an art recognized double stranded DNA denaturation method suitable for the purpose of subsequent hybridization with other nucleic acid molecules. Hence, M.P.E.P. § 2144.07 is not applicable.

Moreover, M.P.E.P. § 2144.09 pertains to close structural similarity between chemical compounds and is irrelevant to the Examiner's 35 U.S.C. § 103 rejection.

Because a *prima facie* case of obviousness has not been made, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 2, 4, 6-8 and 41 under 35 U.S.C. § 103.

***Claims 1-3 and 41***

Claims 1-3 and 41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zarling *et al.* in view of Yoshida (*Biochem. Biophys. Res. Comm.*, 116: 217-221 (1983)). *See* Office Action, page 5, paragraph 8. In particular, the Examiner alleges that

it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant comprising polyamino acids in view of the prior art of Zarling *et al.*, and Yoshida. One having ordinary skill in the art would have been motivated to do so because Yoshida has successfully used an amino acid denaturant (i.e., poly-L-glutamic acid) to denature a double stranded nucleic acid probe into a single stranded and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Yoshida) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

*See* Office Action, page 6, lines 7-18. Applicants respectfully traverse this rejection.

As stated above, the Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. Here, a *prima facie* case of obviousness has not been made because there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Zarling *et al.* or to combine Zarling *et al.* with Yoshida to arrive at the claimed methodology. The Examiner has acknowledged that Zarling *et al.* fails to disclose denaturing "double stranded nucleic acid molecules using an amino acid denaturant comprising polyamino acids as recited in claims 1-3 and 41." *See* Office Action, page 5, last two lines. Moreover, Yoshida makes no reference to denaturing double stranded DNA for the purpose of subsequent hybridization of the strands to different nucleic acid molecules. Absent the teachings in Applicants' specification, the skilled artisan would not regard the denaturation methodology of Yoshida as a substitute or useful in the hybridization methodology discussed by Zarling *et al.* Applicants respectfully assert that the Examiner has improperly relied upon hindsight reasoning.

Relying upon M.P.E.P. §§ 2144.07 and 2144.09, the Examiner alleges that motivation to utilize the denaturation method disclosed by Yoshida in the methodology disclosed by Zarling *et al.* "arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose." *See* Office Action, paragraph bridging pages 6-7. However, as discussed above, Yoshida does not describe an art recognized double stranded DNA denaturation method suitable for the purpose of subsequent hybridization with other nucleic acid molecules. Hence, M.P.E.P. § 2144.07 is not applicable.

Moreover, M.P.E.P. § 2144.09 pertains to close structural similarity between chemical compounds and is irrelevant to the Examiner's 35 U.S.C. § 103 rejection.

Because a *prima facie* case of obviousness has not been made, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-3 and 41 under 35 U.S.C. § 103.

***Claims 6-8***

Claims 6-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zarling *et al.* in view of Yoshida as applied to claims 1-3 above. *See* Office Action, page 7, paragraph 9. In particular, the Examiner alleges that

it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used an amino acid denaturant with different concentrations in the method as recited in claim 1 in view of prior art of Zarling *et al.*, and Yoshida. One having ordinary skill in the art has been motivated to do so because optimization of concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimize concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid.

*See* Office Action, paragraph bridging pages 7-8. Applicants respectfully traverse this rejection.

As stated above, the Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. For the reasons stated above and fully incorporated here (*see* above section headed "***Claims 1-3 and 41***"), a *prima facie* case of obviousness has not been made because there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in



the art, to modify Zarling *et al.* or to combine Zarling *et al.* with Yoshida to arrive at the claimed methodology.

Moreover, a *prima facie* case of obviousness has not been made because neither the references alone or in combination teach or suggest all the claim limitations. In particular, claims 6-8 are dependent upon claim 1 and respectively require an amino acid denaturant in the range from 1 mM to 500 mM, 5 mM to 50 mM, or having a value of about 10 mM respectively. Moreover, the Examiner acknowledges that "Zarling *et al.*, and Yoshida do not disclose . . . a concentration of amino acid denaturant as recited in claims 6-8." *See* Office Action, page 7, lines 9-10. Furthermore, the Examiner has alleged that "the concentration of the added poly-L-glutamic acid was 4.26  $\mu$ M (150  $\mu$ g in 4 mL of the sample solution)." *See* Office Action, page 7, lines 16-17. This value is *three orders of magnitude* outside of the claimed ranges. Hence, the applied references clearly do not include all of the claimed limitations.

Because a *prima facie* case of obviousness has not been made, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 6-8 under 35 U.S.C. § 103.

***Nonstatutory Obviousness Type Double Patenting Rejection***

Claims 1-4, 6-8 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Pat. No. 6,268,133 in view of Zarling *et al.* in further view of Yoshida. *See* Office Action, page 9, paragraph 11. Applicants thank the Examiner for pointing out that "[a] timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome

an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application." *See* Office Action, page 8, in the paragraph bridging pages 8-9. Applicants respectfully traverse and request reconsideration and withdrawal of the Double Patenting Rejection. However, in the event that the Examiner is unwilling to reconsider and withdraw this rejection, Applicants respectfully request that the Examiner hold this Double Patenting Rejection in abeyance until all other rejections are withdrawn.

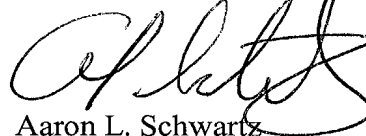
***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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